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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/484,786	06/07/1995	BERNARD F. MACH	MACH-2-CONT.	4894

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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/484,786	Mach et al
Examiner	**Art Unit**
Jehanne Souaya	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 10, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *76-102* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *76-102* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 34
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Jehanne Souaya.

2. This office action is in response to the papers filed May 21, 2002 and the declaration filed June 10, 2002. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following office action contains a new ground of rejection under 35 USC 112/first paragraph. Therefore, this action is NON-FINAL. The office action constitutes the complete set of rejections being presently applied to the instant Application. Response to Applicant's arguments follow.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Double Patenting

4. Claims 76-102 stand rejected under the judicially created doctrine of obviousness -type double patenting as being unpatentable over claims 1-10 of US Patent No. 5,503,976. This rejection is maintained pending the filing of a terminal disclaimer.

Claim Rejections - 35 USC § 112

5. Claims 76-79 and 82-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 76-77 are broadly drawn to an HLA-DR typing method by hybridizing a DNA sample with a sequence that can hybridize to a polymorphic region of an HLA-DR beta chain locus wherein the sequence encodes amino acids 8-14, 26-32, and 72-78. Claims 78-79 are broadly drawn to an HLA-DR typing method in which sample DNA is hybridized to a DNA sequence encoding "a majority" of the region defined by amino acids 8-14, 26-32, 39-45, or 72-78 of a polypeptide encoded by DR-beta-A, DR-beta-B, or DR-beta-C or allelic variants. Claims 86, and 87-93 are depending upon these claims. Claims 94-102 are drawn to kits containing a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the polymorphic region encodes amino acids 8-14, 26-32, and 72-78 and allelic variants or a sequence which can hybridize to a conserved region of an HLA-DR-beta locus at amino acids 39-45.

The specification has described polynucleotides consisting of DR-beta-A, -B, and -C and described the regions with the polypeptide encoded by these polynucleotides, i.e. amino acids 8-14, 24-32 and 72-78 which are variable between -A, -B, and -C and a region which is conserved between -A, -B, and -C, that is amino acids 39-45 and describes methods of using these

polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition, including polynucleotides containing genomic DNA that have not been taught or described in the specification. Since the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the recitation in the claims is large with no common structural feature other than amino acids 38-45 (it is noted that amino acids 8-14, 24-32, and 72-78 are variable between -A, -B, and -C), the three species described in the specification are not representative of the broadly claimed genus. Furthermore, the prior art does not provide compensatory structural or correlative teachings that would enable the skilled artisan to identify or predict the nucleotide composition of the large number of sequences encompassed for use in the methods.

The claims encompass typing methods in which the DNA minimally encoding all or part of amino acids 8-14, 26-32 or 72-78 of any HLA-DR-beta chain is used to determine one or more HLA alleles. However, the specification has only described three specific DR-beta chain coding sequences. Because of the polymorphic nature of these genes, there may be many different DR-beta chain sequences of which three is not representative. Furthermore, the claims, as written encompass using genomic sequences as well as the cDNA sequences, but the genomic DNA sequence has not been described in the specification to establish that applicant was in possession of genomic sequences at the time of filing. Additionally, the claims are drawn to methods using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the

genus of DNA sequences which can be used in the method even larger. The large genus of sequences identified by the broad scope of "hybridization" (ie: large range of hybridization conditions) would not all predictably have the same structural characteristics as the disclosed species because there is no way to determine what variations would be tolerated without trial and error analysis to determine what variations could be made without making the method inoperable as a typing method. Further, the specification provides no teaching or description as to which positions within the regions taught in the specification, including the conserved region, can be altered or varied such that the regions are still characteristic of HLA-DR-B alleles. The specification has not set forth a functional correlation between the different structures encompassed by the method such that a predictable correlation can be made with regard to which variations can and cannot be used for typing.

Although the specification teaches that amino acids 38-45 are conserved, and teaches the polymorphic sequences of amino acids 8-14, 26-32, and 72-78 for the -A, -B, and -C alleles, the claims are not limited to such sequences but instead to undisclosed sequences whose nucleotide composition can vary in these regions as well as other regions of HLA-DR-beta, including genomic DNA sequences (all claims encompass DNA sequences which include such genomic sequences, or methods of using such DNA sequences), which have not been taught or described in the specification. Such recitations in the claims include: "allelic variants" (claims 76-79, 94-98, and the claims which depended therefrom), sequences encoding a "majority of the amino acids in the region" (claims 78-79, and claims which depend therefrom), "sequences capable of

hybridizing to" (claims 76-79, 82-93, 95-98 and 100-102), " a region consisting essentially of amino acids 39-45" (claims 84-85, 101, and sequences which depend therefrom). Claims 78-79 are not supported by the description in the specification because the claims encompass a typing method using a DNA sequence which minimally, encodes "a majority" of a region of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C, or allelic variants. The DNA sequences used in the claim methods include a very large genus of sequences including genomic sequences, coding sequences for DR-beta chains, different from those described in the specification as well as sequences which do not encode the same "conserved" region taught in the specification as a result of the language used such as "sequences capable of hybridizing to" and " a region consisting essentially of amino acids 39-45" . The claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 and 72-78 of DR-beta, -A, -B, and -C of this application, but instead encompass large DNA sequences which only contain a few amino acids from these regions. The DNA sequence is not even limited to coding for the same amino acids as in the described regions because the claims recite that DNA encodes a majority of the region defined by amino acids or "is capable of hybridizing to" these regions, or is an "allelic variants", which allows for considerable nucleotide and amino acid variation from the sequences disclosed in the specification. The three polymorphic sequences described do not constitute a representative number of species of the claimed genus of nucleotides which include variants in the described regions, sequences that hybridize to the sequences disclosed, sequences from other species, allelic variants, and genomic

sequences. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification has not taught which sequences within these regions can be changed and still be useful in a typing method. While the sequence of each nucleic acid in the claimed genus need not be disclosed to fulfill the written description requirement, to establish that applicants were in possession of such changes the specification should describe what changes are encompassed by the full scope of the claims and provide a correlation between the structure of the alterations encompassed by the claims and whether they would be considered HLA-DR-beta alleles and be used for typing . University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The response and declaration provide an alignment of HLA-DR-beta sequences known up to 2002. From this alignment, it is clear that amino acids in each of the 4 regions taught in the specification can be varied, however the specification has not taught or described a predictable correlation between which positions can be varied in such regions and be considered HLA-DR-

beta alleles and still be used for typing. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) With the exception of sequences disclosed in the specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Accordingly, the specification lacks adequate written description for the methods and kits of claims 76-79 and 82-102.

Response to Arguments

6. The response traverses the rejection and provides a declaration by Dr. Strominger to attest to the skill in the art at the time of filing. The arguments, amendments, and declaration have

been thoroughly reviewed but were not found persuasive for the reasons which follow. The declaration and the response set forth that a person of skill in the art as of the July 30, 1982 filing date would have understood the utility of the present invention and known how to exploit the three polymorphic regions and one conserved region taught in the instant specification. This argument has been thoroughly reviewed but was not found persuasive. Firstly, with regard to the usefulness of the sequences, the previous office action did not set forth any rejections based on 35 USC 101. Secondly, the manipulation required by the skilled artisan to determine which sequences within the disclosed regions could be manipulated was not taught in the specification at the time of filing, nor did the art provide correlative teachings to make up for the deficiencies in the specification. The functional characteristics of the disclosed sequences are taught with regard to the complete structure of the regions, the specification does not correlate which sequences within the regions or outside the regions can be varied and still be used for typing HLA. This is exemplified by the number of HLA-DR-beta sequences shown in exhibit K of the response which have variations within the "conserved" region of amino acids 39-45 (14) as well as the number of sequences which have variations within the polymorphic regions of amino acids 8-14, 26-32 or 72-78. The declaration asserts that given the knowledge that multiple HLA alleles most likely existed a person of skill in the art would have understood that highly conserved DNA sequence and 3 polymorphic DNA sequences would be useful for identification and characterization of additional HLA-DR-beta chain alleles. This was not found persuasive as the utility of the claimed invention or the described sequences has not been questioned. The

declaration asserts that Dr. Strominger is of the opinion that the DNA sequences of the conserved region of the instant application could be used to probe cDNA libraries to identify additional HLA-DR-beta chain alleles. This argument has been thoroughly reviewed but was not found persuasive. As stated previously, the office action does not question the utility of the disclosed sequences. However, as stated above, and in previous office actions, the specification does not teach or describe the large number of variations that are present, for example: within the 'conserved" region, such that the skilled artisan would have known, given the specification's disclosure, which sequences could be varied and still be representative of HLA-DR-beta alleles and used for typing. The sequences provided in exhibit K of the response teach sequences that have variant residues within the "conserved" region of amino acids 39-45, and variant residues with regard to the sequences disclosed in the specification for regions 8-14, 26-32, and 72-78. The specification does not teach or describe any functional correlation between these specific positions or variants such that the skilled artisan would have determined from the specification's disclosure what the identity of these sequences would be, if they could be used for typing, or whether they would be considered DR-beta alleles (for example: the DRB4 alleles contain considerable variation in the regions of amino acids 8-14, 26-32, 39-45 and 72-78 from those disclosed in the instant specification). It's unclear how the skilled artisan could have known the identity of such sequences or the 3 out of 7 variations within the "conserved" region of amino acids 39-45, given the disclosure and description in the specification.

In response to the examiner's reliance on Vas-Cath, the response asserts that the identification of the amino acid regions of 8-14, 26-32, and 72-78 as well as the conserved region served as the common structural features that led to the identification of over 300 additional HLA-DR-beta alleles. This argument has been thoroughly reviewed but was not found persuasive because the claims encompass nucleic acid sequences, as well as methods of using such, which included variants which were not described or taught in the specification. A correlation between the structural variations within the sequences disclosed or by "a majority" of the sequences disclosed or with regard to "allelic variants" of the sequences disclosed and a common function was not described or demonstrated at the time of filing. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Further, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The response further traverses the examiner's assertion made in the "response to arguments" of the previous office action, that the amended claims are not limited to the embodiments described in the specification because "any DNA can hybridize to any other DNA molecule under low stringency conditions". The response cites Dr. Strominger's declaration which agrees with Dr. Lathe's description of the state of hybridization based molecular biology as of July 30, 1982, in the declaration submitted by Dr. Lathe. These arguments and assertions have been thoroughly reviewed but were not found persuasive for reasons made of record above. To reiterate, the claim are drawn to nucleic acid sequences, and to methods of using nucleic acid sequences which are claimed broadly such that they encompass sequences with considerable variations as compared to the sequences of the claimed invention. Because the specification does not teach or describe such variations or how such variations would correlate specifically for typing methods, ie: variants characteristic of DRB1, DRB3, DRB4, or DRB5 alleles which were later identified, the fact that they may isolated using the sequences disclosed does not set forth a description of the DNA itself. As set forth in University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405: "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606. The

specification, for example, has not taught the variations within the DRB-4 alleles which were later identified (for example within the conserved region of amino acids 39-45), such that the skilled artisan would have known at the time of filing that such variations would still be DR-beta alleles. Further, the specification has not taught what variations can be made to regions 8-14, 26-32 or 72-78 and still be an "allelic variant" of the disclosed sequences.

With regard to the traversal concerning the Examiner's statement that full length DR-A, DR-B, and DR-C sequences would be useful for HLA-typing (made in the previous Examiner's "Response to Arguments"), such arguments will not be addressed as this statement is not reiterated.

New Grounds of Rejection

7. Claims 76-79 and 82-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

8. Claims 76-79 and 82-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 76-77 are broadly drawn to an HLA-DR typing method by hybridizing a DNA sample with a sequence that can hybridize to a polymorphic region of an HLA-DR beta chain locus wherein the sequence encodes amino acids 8-14, 26-32, and 72-78. Claims 78-79 are broadly drawn to an HLA-DR typing method in which sample DNA is hybridized to a DNA sequence encoding "a majority" of the region defined by amino acids 8-14, 26-32, 39-45, or 72-78 of a polypeptide encoded by DR-beta-A, DR-beta-B, or DR-beta-C or allelic variants. Claims 86, and 87-93 are depending upon these claims. Claims 94-102 are drawn to kits containing a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the polymorphic region encodes amino acids 8-14, 26-32, and 72-78 and allelic variants or a sequence which can hybridize to a conserved region of an HLA-DR-beta locus at amino acids 39-45.

The specification has described polynucleotides consisting of DR-beta-A, -B, and -C and described the regions with the polypeptide encoded by these polynucleotides, i.e. amino acids 8-14, 24-32 and 72-78 which are variable between -A, -B, and -C and a region which is conserved between -A, -B, and -C, that is amino acids 39-45 and describes methods of using these polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition. Since the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the broad scope of the claims is enormous with no common structural feature other than amino acids 38-45 (it is noted that amino acids 8-14, 24-32, and 72-78 are variable between -A, -B, and -C), the three sequences described in the specification are do not enable the skilled artisan to make or use the broad scope of the claimed invention without undue experimentation. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable the skilled artisan to identify or predict the nucleotide composition of the large number of sequences encompassed for use in the methods.

The claims encompass typing methods in which the DNA minimally encodes amino acids 8-14, 26-32 or 72-78 of any HLA-DR-beta chain is used to determine one or more HLA alleles. However, the specification has only described three specific DR-beta chain coding sequences. Because of the polymorphic nature of these genes, there may be many different DR-beta chain sequences, which the specification does not teach. Additionally, the claims are drawn to methods

using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. The large genus of sequences identified by the broad scope of "hybridization" (ie: large range of hybridization conditions) would not all predictably have the same structural characteristics as the disclosed sequences because there is no way to determine what variations would be tolerated without trial and error analysis to determine what variations could be made, for example, within the "conserved region, such that the nucleic acids would still be HLA-DR-beta alleles and useful for typing HLA-DR-beta. Although hybridization methods were known and used in the art at the time of filing, such hybridization methods, to identify the variants encompassed by the broadly claimed invention, are unpredictable with regard to what variations encompassed by the broadly claimed invention would be useful for typing HLA-DR-beta. Further, the specification has not set forth a functional correlation between the different variations within the disclosed structures encompassed by the method such that a predictable correlation can be made with regard to which variations can and cannot be used for typing, or which variations could be made and still be encompassed by the broadly claimed nucleic acid sequences.

Although the specification teaches that amino acids 39-45 are conserved, and teaches the polymorphic sequences of amino acids 8-14, 26-32, and 72-78 for the -A, -B, and -C alleles, the claims are not limited to such sequences but instead to undisclosed sequences whose nucleotide composition can vary in these regions as well as other regions of HLA-DR-beta, including genomic DNA sequences (all claims encompass DNA sequences which include such genomic

sequences, or methods of using such DNA sequences), which have not been taught or described in the specification. Such recitations in the claims include: "allelic variants" (claims 76-79, 94-98, and the claims which depended therefrom), sequences encoding a "majority of the amino acids in the region" (claims 78-79, and claims which depend therefrom), "sequences capable of hybridizing to" (claims 76-79, 82-93, 95-98 and 100-102), " a region consisting essentially of amino acids 39-45" (claims 84-85, 101, and sequences which depend therefrom). Claims 78-79 are not supported by the description in the specification because the claims encompass a typing method using a DNA sequence which minimally, encodes "a majority" of a region of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C, or allelic variants. The DNA sequences used in the claimed methods include a very large genus of sequences including genomic sequences, coding sequences for DR-beta chains, different from those described in the sequence as well as sequences which do not encode DR-beta changes as a result of the language used such as "sequences capable of hybridizing to" and " a region consisting essentially of amino acids 39-45" . The claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 and 72-78 of DR-beta, -A, -B, and -C of this application, but instead encompass large DNA sequences which only contain a few amino acids from these regions. The DNA sequence is not even limited to coding for the same amino acids as in the described regions because the claims recite that DNA encodes a majority of the region defined by amino acids or "is capable of hybridizing to" these regions, or is an "allelic variants", which allows for considerable nucleotide and amino acid variation from the sequences

disclosed in the specification. The specification has not taught which positions within these regions can be changed and still be HLA-DR beta alleles and useful in a typing method. The response and declaration provide an alignment of HLA-DR-beta sequences known up to 2002. From this alignment, it is clear that amino acids in each of the 4 regions taught in the specification can be varied, however the specification has not taught or described a predictable correlation between which positions can be varied within such regions, including the "conserved" region and still be used for typing or which positions can be varied within the disclosed regions and still be identified as DR-beta alleles. As the art does not provide any correlative teachings to make up for the deficiencies in the specification, the skilled artisan would be required to perform trial and error analysis to establish a predictable correlation between the variations in nucleic acids used in the broadly claimed methods and encompassed by the broadly claimed kits and the identity of HLA-DR-beta alleles which can tolerate such variations.

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
12/12/02

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600